A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of the degree of

M.Ch (UROLOGY) – BRANCH – IV

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AUGUST 2013

DECLARATION

I solemnly declare that this dissertation titled **"A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS"** was prepared by me in the Department of Urology, Madras Medical College and Rajiv Gandhi Government General Hospital, Park town, Chennai - 3 under the able guidance and supervision of **Prof.R.Jeyaraman, M.S., M.Ch (Uro).,** Professor & Head of the Department, Department of Urology, Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch. Urology.

Dr.SURESH KUMAR.N

Place: Chennai
Date:

CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS"** submitted by **Dr.Suresh Kumar.N** appearing for **M.Ch. (Urology)** degree examination in August 2013, is a bonafide record of work done by him under my guidance and supervision in fulfillment of requirement of The Tamil Nadu Dr.M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

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APPENDIX-3

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. N. Suresh Kumar
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Dear Dr. N. Suresh Kumar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study of association between metabolic syndrome and nephrolithiasis " No.25032012.

The following members of Ethics Committee were present in the meeting held on 22.03.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer
6.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

APPENDIX-5
ABBREVIATION

CT	:	Computed Tomography
USG	:	Ultrasonogram
WC	:	Waist Circumference
FBS	:	Fasting Blood Sugar
SBP	:	Systolic Blood Pressure
DBP	:	Diastolic Blood Pressure
TGL	:	Triglycerides
HDL	:	High Density Lipoprotein
MSC	:	Metabolic Syndrome Components

INTRODUCTION

Urinary stone disease is a common disease affecting mankind and it was described since historical times. The life time risk of developing stone disease was 1% to 15 % [1]. It varies between races, geographical area of living, age[2], gender, occupation etc... Generally there is increased prevalence of stone disease in western countries when compared to south Asian countries, but due to westernization of culture in these countries there is increased incidence of nephrolithiasis.

Nephrolithiasis were polycrystalline aggregates containing various proportions of crystal and organic matrix components. The common nephrolithiasis calculus were calcium oxalate stones, calcium phosphate stones,uric acid stones,calcium magnesium ammonium phosphate stone (triple phosphate stone or struvite stone) and cystine stone.

Due to advances in the investigation modalities for the diagnosis of nephrolithiasis, stone disease was increasingly diagnosed prior to their symptomatic presentation. And also due to marked advancement in technology, nephrolithiasis were increasingly treated by non invasive methods like Extra corporial

Lithotripsy (ESWL) and by minimal invasive procedures like Per cutaneous nephrolithotomy (PCNL). These procedures treat the nephrolithiasis patients with less morbidity and with good results.

Because of profound morbidity due to the disease and during treatment, loss of renal function with end stage renal disease in some neglected cases and increased cost of expenditure for diagnosis and treatment, there was shift of focus from treatment to prevention of nephrolithiasis.

The development of nephrolithiasis was most likely a multi factorial process and it is not fully addressed by current theories.

Metabolic syndrome[3] is a complex of medical disorders; when they occur together have clinical significance like increased risk of developing cardiovascular disease, cerebrovascular accidents, diabetes mellitus (type two) and atherosclerosis. There are different definitions for defining metabolic syndrome and they all include the main components – obesity or waist circumference, hypertension, hyperlipidemia and hyperglycemia.

The associations of metabolic syndrome with nephrolithiasis were showed by many studies[4] in a defined population. The exact patho -physiology of this association was not clear, but shown to be

associated with metabolic syndrome patient's urinary constituents like decrease in urinary PH, increased urinary calcium and uric acid excretion and decreased excretion of urinary citrate which is an important inhibitor of nephrolithiasis.

We investigate this association in patient population in our institute with nephrolithiasis and compare with individuals without nephrolithiasis.

AIM AND OBJECTIVE

The aim of this study was

- To evaluate the relationship between metabolic syndrome and nephrolithiasis

- To evaluates the relationship between each metabolic syndrome constituents with nephrolithiasis.

REVIEW OF LITERATURE

Renal calculus disease can be divided in to two broad groups on the basis of location of calcification in kidney. Nephrolithiasis was the term used to describe presence of calculus in renal pelvic calyceal system. The presence of calculus in the renal parenchyma was termed as nephrocalcinosis. The word “calculus” is derived from Latin that means “pebble”. Nephrolithiasis affected mankind more than a thousand years. A 1.5 cms size nephrolithiasis was noted in an Egyptian mummy in a tomp dated 4400 B.C[5]. Although nephrolithiasis found in human in the ancient time, only in the past 200 years it was investigated and analysed on scientific basis. The chemical constituents of urinary calculus was first described with uric acid stones and was called acid of calculus or lithic acid (Greek word lithic means stone) .

From ancient history the treatment of stone disease had progressed from portions and prayers to external application (hot water) [6] to destructive treatment (nephrectomy for nephrolithiasis and its sequel) to curative treatment (removal of stone by surgery) to preventive treatments.

For making diagnosis of nephrolithiasis it is crucial to have imaging instruments. The first important event was the invention of X- ray by Roentgen in 1895. The first radiograph showing nephrolithiasis was taken by John Macintyre, a Scottish physician in 1896. By using plain X- ray film, nephrolithiasis were classified in two types: Radio opaque calculus and radiolucent calculus depending on the presence of calcium[7]. Calcium containing calculus like calcium oxalate, calcium phosphate, Struvite or triple phosphate calculi were radio opaque on plain film. They account to 90% of the renal calculus disease. Cystine stones were moderately radio opaque when compared to calcium containing stone and have homogenous ground glass opacity. The radio opacity was due to high physical density, high atomic number and sulphur content[8]. Pure uric acid calculus, matrix calculus and xanthine calculus were radio lucent.

The functional and anatomical studies of urinary tract were done after the invention of iodinated contrast material 'uroselectan' by Moses Swick et al in 1928[9]. Intra venous Urography confirms the intra renal location of calculus and tells about exact location of calculus in relation to pelvic calyceal anatomy which was used in

the management of nephrolithiasis and also shows presence of anatomical abnormality which predispose to calculus formation.

The use of ultrasonogram in medicine begins after Second World War. The first published work on medical use of ultrasonogram was done by Dr. Theodore Dussik[10] in Austria on transmission of ultrasound waves during his imaging of brain. Another scientist named Professor Ian Donald of Scotland improved the technology and devised practical technology and ultrasound application in clinical use in 1950. Ultrasonography was an important imaging modality in the diagnosis and the localization of nephrolithiasis. Ultrasound imaging results from interaction of sound waves with tissues and other structures in body. The frequency of sound waves used in Urology was 3.5MHz to 5MHz.

Image production in ultrasonography starts with transducer. Transducer used here has two functions as producer of ultrasonic waves and also as receiver of reflected mechanical sound. These received sounds were converted into electrical energy which was in turn converted into image by ultra sound machine. Gray scale B mode ultrasonography was commonly used in Urology producing real time two dimensional images containing shades of gray. Most of the renal calculi were seen as bright echogenic foci with post

acoustic shadow. Even radiolucent uric acid and xanthine calculus were visualized using this modality with the exception of Indinavir calculus[11] in patients with AIDS. Matrix calculus was visualized as echogenic foci without post acoustic shadow[12].

Middleton et al [13] concluded from their study that Ultrasonographic ability to diagnose nephrolithiasis was influenced by calculus size but not calculus position or obesity of the patient. For better visualization of renal calculus focal zone should be kept at depth of the stone or slightly deeper. In this study they showed 100% sensitivity for visualizing calculus of size 5mm or more, 96% sensitivity for calculus of size 2.6mm to 5mm and 85% for calculus of size less than 2.5mm. Again real time imaging was more sensitive than static images due to difficult to demonstrate post acoustic shadow in static images.

Ultrasonography also used in guiding therapy for nephrolithiasis in extracorporeal shock wave lithotripsy and laparoscopic nephrolithotomy. Ultrasonography has the advantage of non invasive modality and can be used in patients with increased renal parameters, allergy to contrast material and in patients where radiation cannot be used as in pregnancy and also in the follow up.

False positive diagnosis of nephrolithiasis were made in renal arterial calcification and in patients with intra renal gas.

After the invention of computer tomography by Sir Godfrey Newbold Hounsfield [14] in 1940, it became the most commonly used imaging tool for diagnosis of nephrolithiasis. He received noble prize for physics in 1976. Computer Tomography (CT) have better contrast resolution so all stones except pure matrix calculus and Indinavir calculus, appear dense when compared to surrounding soft tissues. Non contrast spiral CT has high sensitivity[15,16] in detecting nephrolithiasis but low specificity because it do not distinguish nephrolithiasis from Randall's plaque and sub mucosal stone. The density of nephrolithiasis can be measured in CT images, which predicts the hardness of the stone. The disadvantages of CT were increased radiation exposure, patients may have allergic reactions and contrast induced nephropathy when contrast was used.

PATHOPHYSIOLOGY OF CALCULUS FORMATION

Nephrolithiasis contains large amount of crystalline material (97%-98%) and organic matrix providing the framework for deposition of crystals[17]. The calculus formation process was a

complex and continuous process that occur as urine filtered from the glomerulus moves along the nephrons. Once calculus was formed they may come out along with urine formed or captured inside the pelvic calyceal system of kidney with promotion of growth.

Calculus formation starts when

1) There is excess excretion of calculus forming salts and precipitation to form nuclei or crystal.

2) There is decrease in substance that inhibits crystal deposition.

3) There is availability of specific macromolecules needed for calculus formation.

A solution containing molecules or ions of difficult solubility salt was called as Concentration Product (CP). It can be mathematically expressed as product of concentration of pure chemical components of that salt. For example CP of sodium chloride was expressed as

$$[NaCl] = [Na+][Cl-]$$

A solution has been considered as saturated when further adding of salt will not cause mixing of solvent in the solution. The

CP at this point of saturation of solution was called thermodynamic Solubility Product (Ksp) , when further crystals were added at this point there will be precipitation unless the solution temperature or pH were altered.

In Glomerular filtrate even when calculus forming salt constituents (calcium oxalate) exceed Ksp, crystallization do not occur due to presence of inhibitors of crystal formation. The calculus formation inhibitors present in urine were citrate, glycosaminoglycan like heparin sulfate, magnesium, RNA, acid mucopolysaccharides and urinary glycoproteins like Tamm Horsfall glycoprotein and nephrocalcin. Citrate was an important inhibitor of nephrolithisis and it acts by

1) It reduces the calcium salts saturation in urine by combining with calcium.

2) Directly prevents calcium oxalate nucleation.

3) It inhibits precipitation and growth of Calcium Oxalate crystals.

4) It enhances Tamm Horsfall glycoprotein's inhibitory effect

These inhibitors allow high concentration of Calcium Oxalate crystals in the state of solution. This point of saturation was called as metastable state. On further increase in salt concentration a stage was reached at which crystal forms in urine. The CP at this state was termed as formation Product (Kf).

Solubility Product (Ksp) and Formation Product (Kf) differentiates urine in three forms.

1) Under saturated

2) Metastable

3) Unstable

In under saturated state of urine (below solubility product) crystal does not form under any period and dissolution of formed crystal was possible. In unstable state of urine (above formation product) crystal will form. Here the supersaturated solution deposits excess crystal material in solution as solid particle and this process was called nucleation[18]. In metastable state of urine (between Formation Product and Solubility Product) spon-taneous nucleation does not form even when the urine was supersaturated.

In this state calculus growth will be possible over an already formed crystal; per se calculus formation will not be possible in the time taken by the urine formed normally in the glomerulus to reach urinary bladder in the pelvis. Here calculus formation occur in some situations like

1) In some areas of nephrons where the local area concentration product (CP) exceeds the formation product (Kf) for prolonged period to favor nucleation to form.

2) When there is local obstruction in the renal pelvis, calyx or ureter, the transit time of urine in kidney will be prolonged causing crystal formation.

3) Microscopic impurities in urine may facilitate nucleation by absorption of crystal components on their surface. Heterogeneous Nucleation thus formed normally requires very less energy than the other form of nucleation.

Nephrolithiasis contains mainly mixed calculus, often a combination of calcium phosphate and calcium oxalate. Normally calcium oxalate crystalli-zation starts by heterogeneous nucleation. Calcium phosphate may serve as nidus. Hydroxyapatite was stable in alkaline urine and the crystal of hydroxyapatite may induce

growth of calcium oxalate monohydrate crystal in a metastable state of urine[19]. Dicalcium phosphate dihydrate was stable form in acidic urine and can induce hetero-geneous nucleation of calcium oxalate calculus [20,21]. From these findings it can be proposed that nephrolithiasis was formed from calcium salts in a metastable urine by heterogeneous nucleation.

The newly formed crystals can be excreted in urine as crystalluria or enlarge to become clinically significant calculus in the kidney. Calculi were much larger in size that cannot be explained only by crystal nucleation theory. So there must be other theory to explain the mechanism of growth of crystal and their containment in kidney to over come their excretion in urine. Crystals will bind with each other by the process aggregation or agglomeration. Here many particles were held - together by inter molecular forces which resist shear forces. Crystalline aggregations were seen to form in the center of urinary calculus particularly in wedellite, whewellite, uric acid and brushite calculus[22]. Nephrolithiasis were usually multi component, have distinct concentric rings when sectioned. Consecutive layers have different components but each layer have homogenous crystalline

composition. Epitaxy was a process of oriented growth of a single crystalline lattice over another crystalline lattice[23].

Calculus analysis shows it contain crystalline and non crystalline component. This non crystalline component was termed as matrix. In nephrolithiasis the matrix commonly account to 2-3 %[24]. In matrix stone the percentage of matrix may be up to 65 %[25,26]. By chemical analysis matrix stone contains 65% hexosamine, 10% water, substance A, nephrocalcin[28], Tamm-Horsfall glycoprotein[29], albumin and glycosaminoglycan[30]. After formation if nucleated crystals were flushed by urine, calculus will not be formed. Crystal retention was an important factor and occurs if it adheres to the urothelium or if it grows to a large size to be trapped in the tubule. The first evidence of crystal retention has been showed by Randall in1940 as plaques of sub epithelial deposits of calcium crystals in renal papillae[31]. These plaques were called Randall's plaques which act as a nidus for urinary calculus formation.

Stoller et al.[32] showed papillary calcifications in 57% of cadaveric kidneys when imaged by using high resolution

radiography. They also observed correlation between papillary calcifications and patient's hypertensive history.

Normal urothelium in the urinary tract have some safety mechanism against nucleation of crystal and attachment of calcium oxalate crystals[33]. When there is chemical injury to the urothelium in kidney, there will be failure of this protective property predisposing to adhesion of calcium oxalate crystals. Normal urothelium has a layer of glycosaminoglycan[34] which prevents adherence of bacteria and prevents adhesion of crystals.

Nephrolithiasis contains mostly calcium (75%). So it was classified in to calcium containing calculus and non calcium containing calculus[35].

Calcium-Containing calculus

- Calcium oxalate – 60%
- Hydroxyapatite- 20%
- Brushite- 2%

Non Calcium Containing calculus

- Uric acid – 7%
- Struvite – 7%
- Cystine -1%

Nephrolithiasis were classified on basis of metabolic derangements or any environmental abnormality. The derangements causing nephrolithiasis with calcium were due to hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia. Cystine calculus was formed due defective absorption of renal cystine. Uric acid calculus was formed in acidic urine and Struvite calculus formed in infective urine where urea splitting organisms like Proteus and Klebsiella cause urine alkalization and calculus formation. For Cystine calculus treatment will be started immediately knowing the chemical composition of the calculus. But in calcium containing calculi, causes were multiple so it was important to understand the underlying metabolic disorders causing the calculus to start the appropriate treatment

Calcium containing calculus

Hypercalciuria

Hypercalciuria was one of the most frequently detected abnormalities found in persons having calcium containing nephrolithiasis. The pathogenic role for hypercalciuria in nephrolithiasis were: 1) in approximately 36% to 66% of individuals with calculus, hypercalciuria was present, 2) medical therapy tends to fail if the patient had persistent hypercalciuria,

3)therapies which reduces urinary calcium level also reduces calculus formation, 4) increased urinary calcium found in patients with nephrolithiasis with Randall's plaque and it was thought as a precursor of calcium calculus. Increased calcium concentrations in urine causes increased urinary calcium salts saturation and reduced urinary calculus inhibitors like urinary citrate.

Pak et al[36] classified the causes of hypercalciuria into three types

- Absorptive hypercalciuria
- Renal hypercalciuria
- Resorptive hypercalciuria

Absorptive Hypercalciuria was defined as increased urinary calcium following oral calcium load due to increased intestinal absorption of calcium. It usually occurs in 55% of calculus forming patients. It was classified into type 1- when urinary calcium excretion was high in spite of low calcium diet and type 2- when urinary calcium level becomes normal when patient was placed in calcium restricted diet.

Renal hypercalciuria

Of the reabsorbed 98% of filtered calcium, 70% of the absorption occurs in proximal tubule mostly by paracellular pathway. So impaired renal absorption leads to increased urinary calcium leads to secondary hyperparathyroidism. The exact cause of renal calcium leak was not found but may be due to renal injuries, structural abnormality or functional defect.

Resorptive Hypercalciuria

It was uncommon and mostly due to primary hyperparathyroidism. Primary hyperparathyroidism was responsible for the formation of nephrolithiasis in 3-5% of cases[37]. Due to increased parathyroid hormone there was increased bone resorption and increased urinary calcium .It also causes increased $1,25(OH)_2$ vitamin D synthesis which in turn increases intestinal calcium absorption and increases serum and urinary calcium. Primary hyperparathyroidism was suspected in nephrolithiasis when serum calcium levels were more than 10.1mgs%. In equivocal cases of serum calcium, ionized calcium and urinary cyclic AMP were measured (both increased in primary hyperparathyroidism). Resorptive hypercalciuria also caused by hypercalcemia of malignancy, vitamin D toxicity, sarcoidosis, and thyrotoxicosis.

Hyperoxaluria

It was defined when urinary oxalate excretion exceeds 40mg/day. Hyperoxaluria[38] divided into

1) ***Primary hyperoxaluria*** **-** when it was caused by genetic defect in the glyoxalate metabolism, where normal metabolism of glyoxalate to glycine does not happen and there is increased oxidative conversion of glyoxalate to oxalate occurs. It leads to increased (>100mgs/day) excretion of urinary oxalates. Primary hyperoxaluria divided in to three types according to the defect. In type 1 the enzyme defect was alanine glyoxylate aminotransferase (AGT) in liver and the patient have increased levels of oxalate and glycolate. In type 2 the enzyme defect was glyoxylate reductase / hydroxypyruvate reductase (GRHPR) in liver and increased formation of L glyceric acid and oxalates. It was less severe form when compared to type 1. In type 3 no enzyme defect isolated till date.

2) ***Enteric hyperoxaluria*** **-** when it was caused by intestinal malabsorbtive state as in inflammatory bowel disease, celiac sprue, intestinal resection surgeries or in bariatric surgeries done for obesity. It was the most common acquired form of

hyperoxaluria. Here due to malabsorption of fat, there was increased saponification of fatty acid with calcium and magnesium leading to decreased availability of calcium to complex with oxalate in intestine. So increased amount of oxalates were absorbed.

3) ***Dietary hyperoxaluria-*** Diets rich[39] in oxalates like nuts, spinach, strawberry, chocolate, broccoli and rhubarb can cause hyperoxaluria. Food with increased animal protein causes increase in urinary oxalate and calcium. Ascorbic acid addition in diet may convert in to oxalates in vivo and increase in urinary oxalates. Calcium restricted diet causes increased oxalate availability in bowel and causes increased urinary oxalate. When there was absent or reduced intestinal colonization of oxalate degrading bacterium (Oxalobacter formigenes) it may lead to increased urinary excretion of oxalates.

Hyperoxaluria causes increased saturation of urinary calcium oxalate and leads to calcium oxalate calculus formation. Oxalate was said to cause crystal growth and crystal retention by renal tubular injury caused by lipid peroxidation and oxygen free radical formation.

Hyperuricosuria

It was defined as when uric acid excretion[40] in urine exceeds 600mgs/day. Only hyperuricosuria as an abnormality was noted in 10% of calcium calculus forming patients without any other abnormalities. At PH above 5.5 hyperuricosuria causes increased formation of calcium oxalate calculus by heterogeneous nucleation. At PH below 5.5 hyperuricosuria causes precipitation of uric acid crystals and formation of uric acid calculus by homogenous nucleation and calcium oxalate stones by heterogeneous precipitation. Hyperuricosuria reduces the effectiveness of urinary inhibitors of calculus formation by binding to urinary glycosasminoglycan like heparin. The common causes of hyperuricosuria were increased purine intake in diet, gout, myeloproliferative disorder, lymphoproliferative disorder, multiple myeloma, pernicious anaemia, polycythemia, thalassemia, partial or complete deficiency of enzyme hypoxanthine guanine phosphoribosyl transferase, enzyme phosphoribosylpyrophosphate synthetase overactivity and renal hypouricemia.

Hypocitraturia

It was defined as when urinary citrare level was below 320mgs/day. Hypocitraturia was present in 20% to 60% in calcium

calculus formers with other associated abnormalities and in 10% as an isolated abnormality. Urinary excretion of citrate[41] was primarily determined by acid base state of the body. Metabolic acidosis causes enhanced renal tubular absorption and decreased citrate synthesis in peritubular cells leading to decreased urinary citrate level. Hypocitraturia was caused by pathological states of acidosis as in distal tubular acidosis, chronic diarrhea state and excessive animal protein ingestion.

Distal renal tubular acidosis[44] was associated with high urinary PH (>6.5), high serum chloride and low level of serum potassium and bicarbonate. Acidosis increases bone resorption and increased renal leak of calcium.There was increased excretion of calcium and phosphate and decreased urinary citrate level favoring calcium phosphate calculus formation. It was confirmed by oral acid load test (ammonium chloride test) as these patients were unable to acidify urine (< 5.5). In chronic diarrhea there was increase intestinal loss of alkali leading to acidosis and subsequent hypocitraturia. Increase animal protein intake causes increased acid production and hypocitraturia. Drugs like thiazide diuretics causes increase in intracellular acidosis and hypokalemia and

hypocitraturia, Enalapril causes hypocitraturia, acidosis and hypokalemia.

Hypomagnesuria

It was associated with other abnormalities in 6% to 11% patient with calculus disease and as an isolated abnormality in 1%. It acts as an inhibitor of calculus formation by complexion with calcium and oxalate salts and also by increasing urinary citrate level. Hypomagnesuria was caused by decreased intake in diet and increased loss in chronic diarrhea disorders.

Uric acid stones

Uric acid stones[40] were caused by three main determinants. They were low urine volume, low PH and hyperuricosuria. Of these low urinary PH was very important and consistent variable for the formation of uric acid calculus. Uric acid calculus forms due to congenital, acquired or idiopathic causes. Congenital causes were disorders involving renal tubular urate transport and uric acid metabolism causing hyperuricosuria. Acquired causes were chronic diarrhea, increased animal protein intake and intake of uricosuric drugs and volume depletion. Patients with gouty diathesis have idiopathic low urinary PH and decreased fractional excretion of uric acid and do not have gout.

The pathogenesis of low urinary PH in idiopathic uric acid calculi was not entirely known and it may be multifactorial. Sakhee et al[42] first noted that normouricosuric patients with pure uric acid calculus were likely to have type 2 diabetes mellitus or had glucose intolerance when compared to normal persons or patients having mixed calculus. Further studies shows that uric acid calculus formers excrete more acid in urine and less citrate in urine. The insulin resistance state was linked to the disorder of ammonium excretion in uric acid stone formers.

Pak et al [43] observed higher prevalence of low urinary pH and uric acid calculus in type 2 diabetes mellitus. The mechanism of low urinary pH produced by insulin resistance was not completely known. Insulin has been shown to promote ammonia genesis in kidney from the substrate glutamine and to stimulate Na+/H+ exchanger in the proximal tubule (responsible for ammonium transport or trapping in urine). In insulin resistance state there will be impaired ammonium production and excretion, so hydrogen ion in urine was un buffered leading to low urinary pH. Other mechanism stated was increased free fatty acid in the blood in diabetes would compete with alpha ketoglutarate(end product of

glutamine metabolism) for entry into Krebs cycle and reduces ammonium production.

Normally there will be alkalization of urine and blood in morning and after meals and was called alkaline tide. Loss of diurnal variation in urinary pH occurs in insulin resistance state and this may cause persistence low urinary pH and uric acid calculus. Acidic pH in urine was promoted by increased endogenous acid production and by dietary means. Net acid excretion (NAE) was high in uric acid calculus formers with type 2 diabetes mellitus than in normal persons after controlling dietary component. These studies show that there was increased acid production as a result of insulin resistance and obesity. The diet content influences urinary pH. Diet rich in animal protein causes acidic urine with increased excretion of undissociated uric acid and decreased excretion of citrate. Uric acid in urine was supersaturated by conditions lowering the urine volume like in individuals exposed to hot climate and in workers working in high temperature.

Cystine calculus

It was caused by cystinuria[45] which was an inherited autosomal recessive disease caused by disorder in intestinal and renal tubular transport of cystine, ornithine, lysine and arginine. Cystine was a dimer and was less soluble than its monomer cysteine. Cystine calculus was rare and accounts to less than 1% of total calculus disease. Cystine crystallization was caused by super saturation and there was no inhibitor for cystine calculus formation.

Struvite calculus

Struvite or magnesium ammonium phosphate calculus was discovered by Swedish geologist and named it as struvite after his mentor H.C.G.Von Struvite. It was formed as a result of urinary infection with urea splitting enzyme urease containing organism such as Proteus. Strvite or triple calculus occurs more commonly in females in the ratio of 2:1 when compared to males. It also occur in patients with increased risk of infection such as elderly, diabetic patients, infants born with congenital urinary tract abnormalities, in those with urinary stasis as a result of urinary tract obstruction, urinary diversion or neurological disorder.

Spinal cord injury[46] patients were increased risk of developing infective calculus and calcium calculus because of

neurogenic urinary bladder and hypercalciuria due to immobility. The other calculi were Xanthine and dihydroxyadenine calculus, matrix calculus, Ammonium acid urate calculus and medication induced calculus. Medication induced calculus was divided into medication that directly promotes calculus formation due to excess ingestion like indinavir, triamterene, guaifenesin, silicate, ciprofloxacin and drugs that promote calcium calculus formation such as furosemide, acetazolamide, bumetanide. Patients with anatomical anomalies associated with urinary obstruction were prone to develop calculus disease. In ureteropelvic junction obstruction the chance of developing urinary calculus was about 20%. In Horse shoe kidneys the chance of getting nephrolithiasis was high due to impaired renal drainage caused by high insertion of ureter and also presence of metabolic derangements especially hypocitraturia. Calculus formation occurs in 40% of calyceal diverticulum patients. Medullary sponge kidney was a disorder having ectasia collecting ducts of kidney. It was associated with nephrocalcinosis and nephrolithiasis in most of the patients.

METABOLIC SYNDROME

Metabolic syndrome was combination of medical disorders when it occurs together then there was increased risk of developing

diabetes mellitus or cardiovascular disease[3] . It was also called as Syndrome X, Insulin resistance syndrome or Reaven's syndrome[47] (named after Gerald Reaven). In his lecture in 1988, he introduced the term 'Syndrome X' in describing insulin resistance syndrome. Prevalence of metabolic syndrome increases with age and it drives the global epidemic of cardiovascular disease and type 2 diabetes mellitus. Metabolic syndrome was defined by some sets of defining criteria by two sources.

A) The International Diabetic Federation (IDF)[48] criteria

B) National Cholesterol Education Program(NCEP)[49] criteria

The defining criteria were similar in both groups except of 2 differences. IDF states that if body mass index was more than 30, central obesity was assumed and no need for measurement of waist circumference, where as NCEP criteria measures waist circumference for measuring obesity. Also IDF uses geography specific variable cut off points for waist circumference while NCEP uses one cut off point for waist circumference measurement regard less of geography of study.

IDF criteria for defining metabolic syndrome were central obesity defined by waist circumference with ethnic specific values

and any two of following: Raised blood pressure: systolic BP >130 mmHg or diastolic BP > 85mm Hg or known hypertensive on treatment, Raised fasting blood sugar >100mg/dl or known diabetic on treatment , Raised triglycerides >150mg/dl and reduced serum HDL cholesterol <40mg/dl in males and <50mg/dl in females or known lipid abnormality patient on treatment.

American Heart Association and National Heart Lung and Blood Institute (AHA/NHLBI) [50] intended to update NCEP ATP III definition of metabolic syndrome and defined metabolic syndrome as the presence of any of the three criteria:

1) ***Waist-*** circumference ≥102 cms in males and ≥ 88 cms in females

2) ***Serum-*** triglycerides >150mgs/100ml or on treatment for lipid disorders

3) ***Serum-***cholesterol <40mgs/dl and <50mgs/dl in women or on treatment

4) ***Systolic-*** blood pressure ≥130 mm of Hg or ***diastolic-*** blood pressure≥ 85 mm of Hg or on any anti-hypertensive drug

5) ***Fasting blood sugar*** ≥100mgs/dl or on any anti diabetic drugs for diabetes mellitus.

Metabolic syndrome and its components were associated with nephrolithiasis. The pathophysiology of this association was not clearly understood, but metabolic syndrome was associated with urinary constituents' changes like decreased citrate, low urinary pH and increased excretion of calcium and uric acid in urine. These changes lead to formation of calcium and uric acid calculus.

Asplin J R[51] et al had observed increased prevalence of obesity in USA due to increased food intake and decreased physical activity. They concluded that there was increased incidence of nephrolithiasis in obese patients. They proposed the causes of this increased incidence can be due to increased amount of calculus forming constituents in diet and altered kidney acid base metabolism. Weight loss procedures done for treatment of obesity have risk of calculus formation. Low carbohydrate diet causes risk of uric acid and calcium containing calculus formation. Bariatric procedures done for obesity have risk of developing calcium oxalate calculus due to hyperoxaluria. So controlled weight reduction should be carried out to prevent this complication.

Taylor EN et al[52] observed increased prevalence of nephrolithiasis in obese patients. They showed relative risk of developing calculus in males over 100kgs was 1.44 when compared to male weighing less than 68kgs. Also obese females have increased relative risk of 1.89 comparing non obese individuals.

Negri AL et al[53] in their study on evaluation of calculus forming constituents in urine in calculus patients found that in obese and over weight patients there was increased excretion of uric acid and oxalates and they have increased risk of developing nephrolithiasis when compared to non-obese persons. They also observed increase in body mass index as age advances in males and female individuals.

Cappuccino FP et al[54] in their prospective study in southern Italy had showed that there was increased incidence of nephrolithiasis in middle aged males and females with systemic hypertension. The real mechanism of calculus formation in hypertensive patients was not well understood. Borghi L et al [55] observed essential hypertensive patients excretes increased amount of calcium, uric acid, oxalate in urine in males. Female essential hypertensive persons excretes increased amount of calcium,

phosphorus, uric acid in their urine. They have increased propensity to form calcium oxalate and calcium phosphate calculus. The causative factors may be due to excessive consumption of animal protein and salts or may be due to overweight.

Iba A et al [56] in their study on a rat model of metabolic syndrome had observed that insulin resistance and metabolic syndrome increases the propensity to form uric acid calculus and also calcium calculus. They noted in their rat model with the increase in body weight, serum triglycerides, blood sugar and insulin there is increased urinary excretion of calcium and uric acid. They also noted there is decreased excretion of citrate in urine with low urinary pH.

Kadlec AO et al[57] evaluated difference in calculus composition due to metabolic syndrome in a retrospective analysis. They found that there is increased incidence of uric acid calculus and very low incidence of calcium phosphate calculus in patients having metabolic syndrome. Morbid obese patients tend to form calcium oxalate calculus. Inci M et al[58] in their analysis had shown that increased body mass index and elevated serum triglycerides and reduced serum HDL which were components of metabolic

syndrome were associated with increased uric acid and calcium oxalate dihydrate-calcium oxalate monohydrate calculus.

Abate N et al[59] evaluated the association of uric acid nephrolithiasis with insulin resistance occurring in metabolic syndrome. He concluded that there was decreased ammonia genesis in kidney leading to decreased urinary pH in insulin resistance patients which promotes uric acid calculus formation in normal uric acid excreting patients.

MATERIAL AND METHODS

TITLE OF THE STUDY

A study of association between metabolic syndrome and nephrolithiasis

PLACE OF THE STUDY

The study was conducted in the Department of Urology, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai-3 with the collaboration of Barnard Institute of Radiology, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai- 3 and Institute of Biochemistry, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai-3.

STUDY DESIGN

Single centre. Prospective case control study.

PERIOD OF STUDY

The study work was carried out from March 2012 to February 2013.

ETHICAL COMMITTEE APPROVAL

The institutional Ethical Committee review board approved this study.

No. 25032012.

INCLUSION CRITERIA

Cases:

Patients with unilateral or bilateral renal calculus

Controls:

Individuals without renal calculus

EXCLUSION CRITERIA

Cases:

- Patients with congenital renal abnormalities
- Acute or Chronic renal failure patients
- Patients with metabolic bone disorder or taking treatment for osteoporosis
- Patients with gout
- Patients with major debilitating disease like cancer
- Patients with complication of calculus disease like Calculus pyelonephritis, pyonephrosis or perinephric abscess
- Pregnancy
- Patients with contracted kidney

Controls:

Patients with previous history of nephrolithiasis and other criteria's are as for the cases.

SAMPLE SIZE

100 cases (Group 1) and 100 control (group 2) patients.

METHOD OF STUDY

Details of the study explained to each and every cases and control patients. Informed consent obtained from all of the cases and control. Patients were evaluated in detail. The details obtained from the patients were recorded in the proforma. Analysis was done with the collected details prospectively.

PATIENT EVALUATION

All the individuals (both the cases and controls) underwent ultrasound evaluation of both kidneys. Nephrolithiasis was diagnosed in ultrasonogram by the appearance of hyperechoic lesion in the pelvic calyceal system of kidney followed by post acoustic shadow. These patients were included in group 1(cases). Patients without nephrolithiasis were included in group 2 (controls). Both groups undergo evaluation for the presence of metabolic syndrome. All cases and control undergo measurement of

waist circumference, their systolic and diastolic blood pressure. Their fasting blood analysed for blood sugar, serum triglycerides and serum HDL cholesterol levels. These details were entered into proforma and analysed.

METHODOLOGY

Ultrasonogram

All patients including all cases and control patients undergo ultrasonogram using Mind Ray machine with 5MHz probe. The presence of calculus was defined by hyperechoic lesion in the pelvic calyceal system followed by post acoustic shadow.

Waist circumference

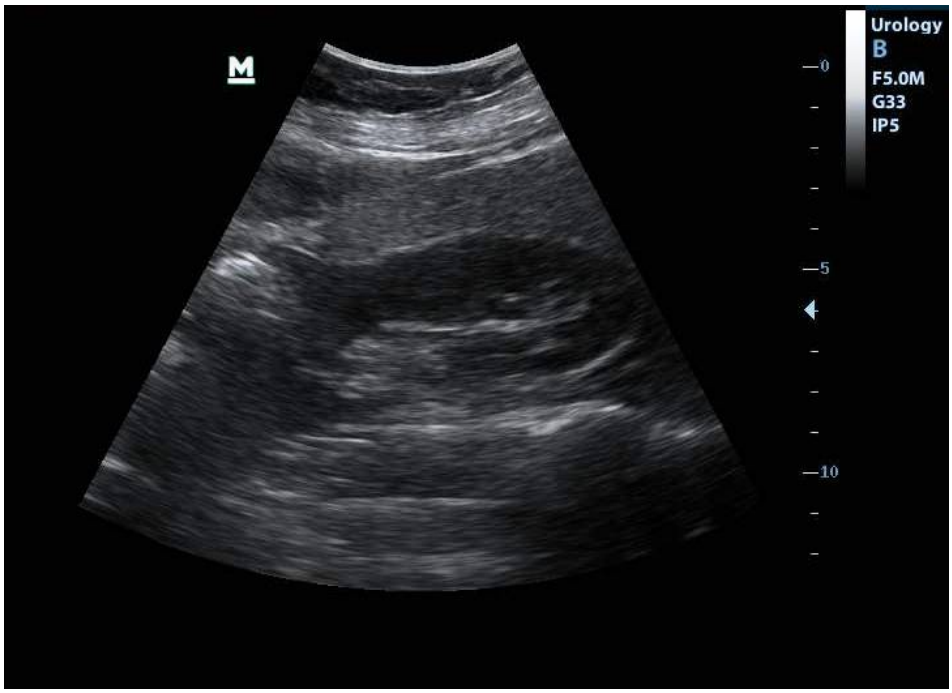
Waist circumference was measured using a non stretchable measuring plastic tape. The measurement was taken with the individuals in a relaxed and standing position with both feet together. Waist circumference measured at midpoint of lowermost border of twelfth rib and upper border of iliac crest at the end of expiration.

Measurement of Blood Pressure

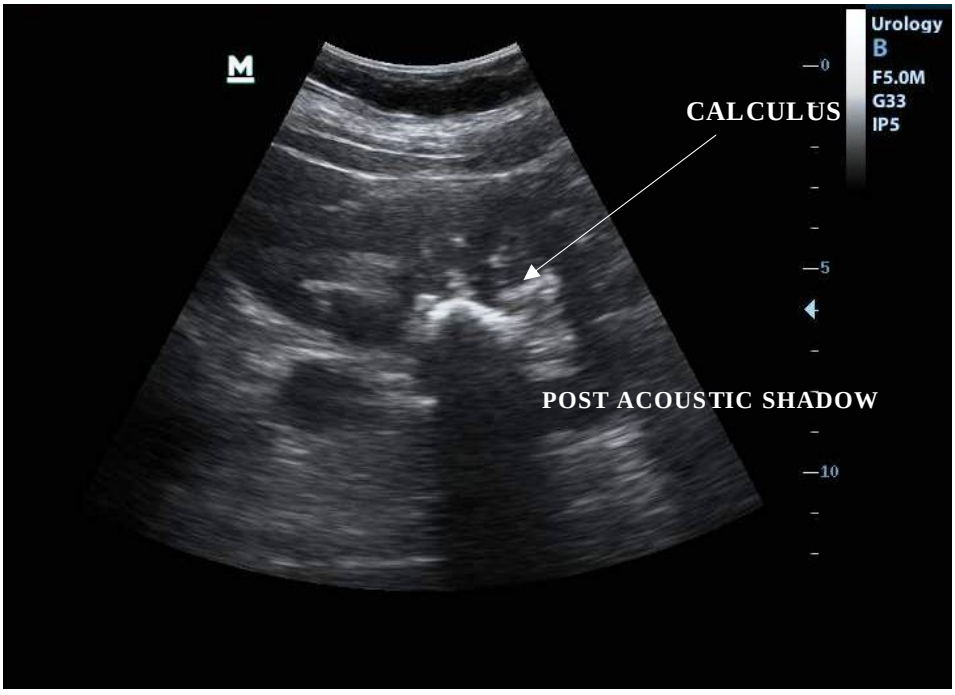
Systolic and diastolic BP was measured using Diamond Deluxe sphygmomanometer. Blood pressure was obtained with the individuals in calm and sitting position. Two readings were taken

with five minutes apart and their average was taken into consideration.

NORMAL RENAL ULTRASONOGRAPHY



ULTRASOUND SHOWING NEPHROLITHIASIS



BIOCHEMICAL TESTS

Fasting venous blood was taken after over night fasting from both cases and control individuals. Plasma fasting sugar was measured by Trinder's glucose activity test or glucose oxidase and peroxidase method using semi auto analyzer – Optima S. Serum triglyceride was measured by Calorimetric analysis using enzymatic analysis by GPO- PAP method using semi auto analyzer Optima S. Serum HDL cholesterol was measured by using direct HDL cholesterol kit by Clearance method using semi auto analyzer OptimaS.

The defining criteria used were based on AHA/NHLBI criteria formed in 2004. The IDF gives Ethnic specific values for the measurement of waist circumference. The cut off point for south Asians were 90 cms for male and 80 cms for female[60]. The presence of metabolic syndrome was defined by presence of 3 or more positive points in the below criteria's:

1) ***Waist-*** circumference ≥ 90 cms in males and ≥ 80 cms in females

2) ***Serum-*** triglycerides > 150mgs/100ml or on treatment for lipid disorders

3) ***Serum***-cholesterol <40 mgs/100ml in males and <50mgs/100ml in females or on treatment for high cholesterol.

4) ***Systolic***- blood pressure ≥130 mm of Hg or ***diastolic***- blood pressure ≥ 85 mm of Hg or on any anti hypertensive drug

5) ***Fasting –serum***- glucose ≥100mgs/100ml or on any drug treatment for diabetes mellitus.

Metabolic syndrome presence in nephrolithiasis group (cases) was compared with metabolic syndrome in normal individuals (controls). Again each component of metabolic syndrome was compared with cases and control.

STATISTICAL METHOD

For discrete data -proportion is computed and the mean and standard deviation are computed for the continuous data.

The chi square test was applied to compare the proportions between the groups to assess the statistical significance.

All analyses were two tailed and $p < 0.05$ was considered significant.

SPSS version 16.0 was used for data analysis.

RESULTS AND OBSERVATIONS

DESCRIPTIVE STATISTICS

Our study consists of 200 individuals who visited our hospital during March 2012 to February 2013. 100 patients were cases (Group 1) with nephrolithiasis and were confirmed by ultra sonogram. Controls (Group 2) were 100 normal persons without nephrolithiasis as confirmed by ultra sonogram or patients with other diseases like urethral stricture, prospective renal donors and urinary tract infections without any evidence of nephrolithiasis in ultra sonogram.

Table-1: The patient characteristics in two groups were shown in Group Statistics

	Group	Number	Mean	Std. Deviation	P-value
Age	Case	100	38.2500	9.67385	0.074
	Control	100	35.6200	10.99015	
Stone Size	Case	100	1.584	0.5120	NA
	Control	100	NA		

P-value <0.05 was significant.

The Mean age group of control (Group 2) was 35.62 $\pm$ 10.99years. The mean age group of cases (Group 1) was 38.25$\pm$9.67 years. Age group between cases and control was comparable and was statistically insignificant (P value >0.05).

In Group 1 (cases) there were 47 females and 53 males. In Group 2(controls) there were 48 females and 52 males.

Table: 2 - Gender difference between two groups

			SEX		Total
			Male	**Female**	
Group	Case	Count	53	47	100
		% within Group	53.0%	47.0%	100.0%
	Control	Count	52	48	100
		% within Group	52.0%	48.0%	100.0%
Total		Count	105	95	200
		% within Group	52.5%	47.5%	100.0%

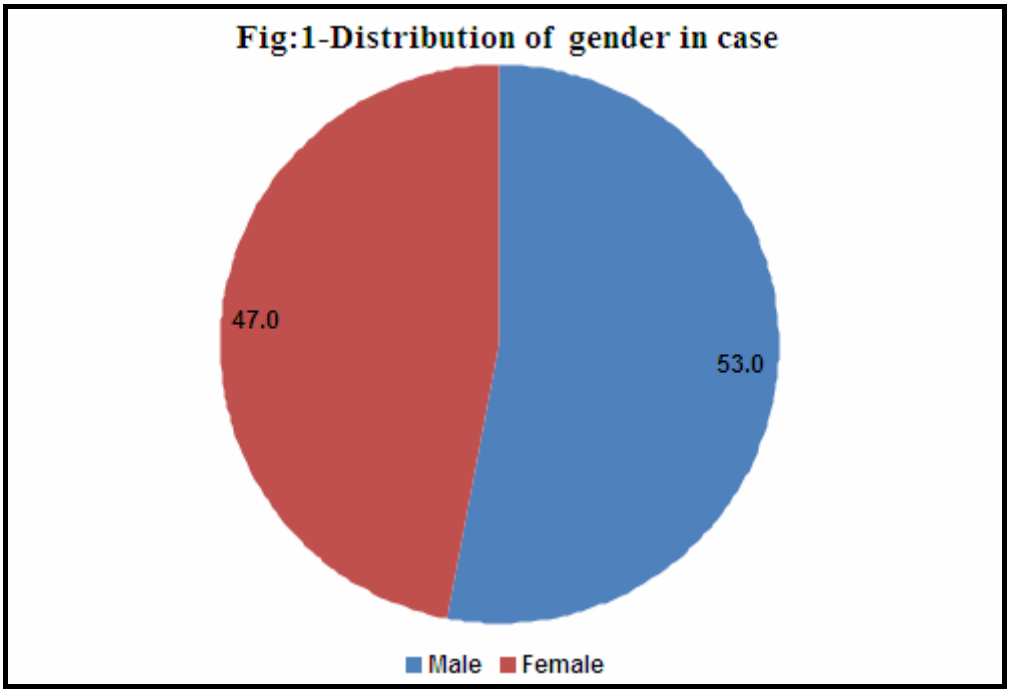
Chi-Square Tests

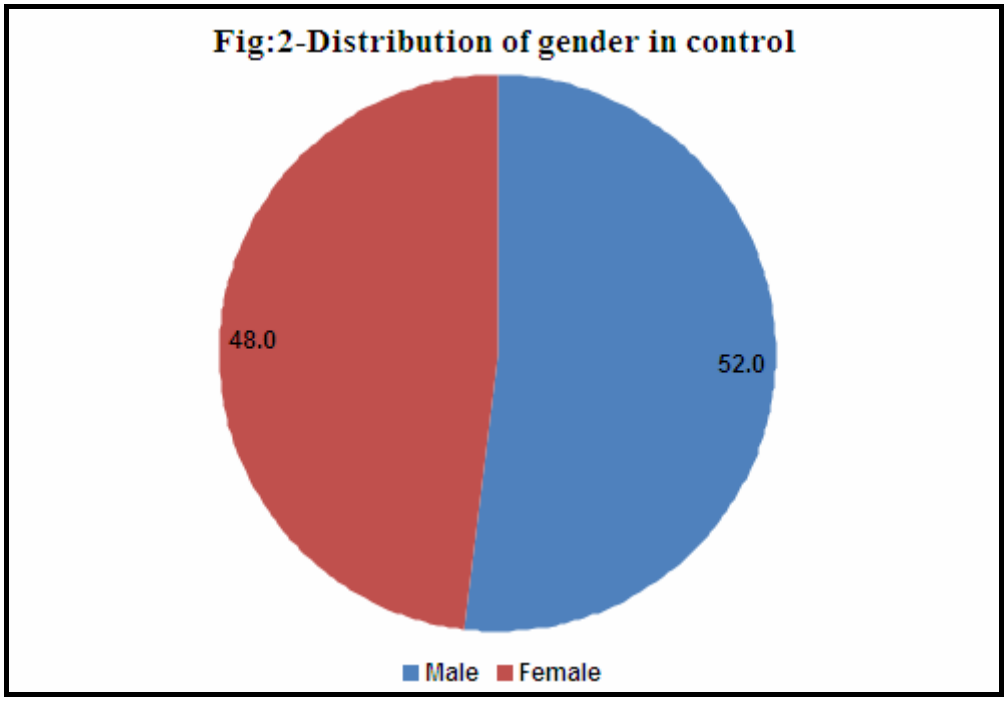
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)(P-value)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.020a	1	.887		
Continuity Correction b	.000	1	1.000		
Likelihood Ratio	.020	1	.887		
Fisher's Exact Test				1.000	.500
Linear-by-Linear Association	.020	1	.888		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 47.50.

b. Computed only for a 2x2 table

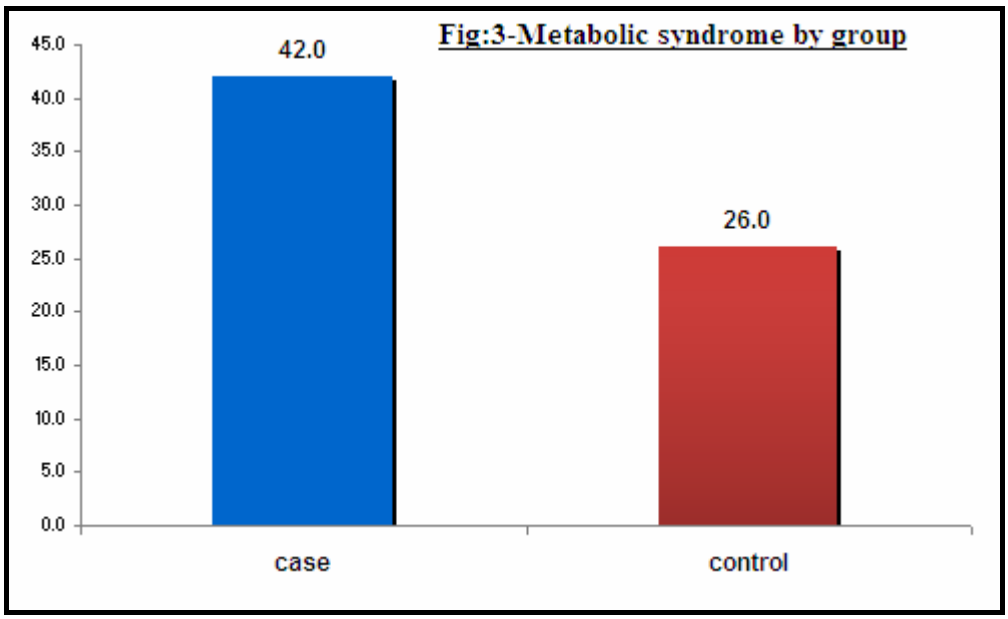
The gender difference between two groups was comparable and was statistically insignificant (P-value> 0.05). (Fig: 1&2)





INTER GROUP COMPARISON

By AHA/NHLBI criteria for metabolic syndrome with Ethnic specific cut off for waist circumference, the number of patients with metabolic syndrome in Group 1 (Cases) was 42(42%) and in Group 2(Control) it was 26(26%) .(Fig: 3)



The metabolic syndrome in two groups were compared by chi square test for test for significance

Table – 3: Metabolic Syndrome

			Metabolic Syndrome group		Total
			Yes	**No**	
Group	Case	Count	42	58	100
		% within Group	42.0%	58.0%	100.0%
	Control	Count	26	74	100
		% within Group	26.0%	74.0%	100.0%
Total		Count	68	132	200
		% within Group	34.0%	66.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)(P-value)	Exact Sig. (1-sided)
Pearson Chi-Square	5.704a	1	.017		
Continuity Correction b	5.013	1	.025		
Likelihood Ratio	5.744	1	.017		
Fisher's Exact Test				0.025	0.012
Linear-by-Linear Association	5.676	1	.017		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 34.00.

b. Computed only for a 2x2 table

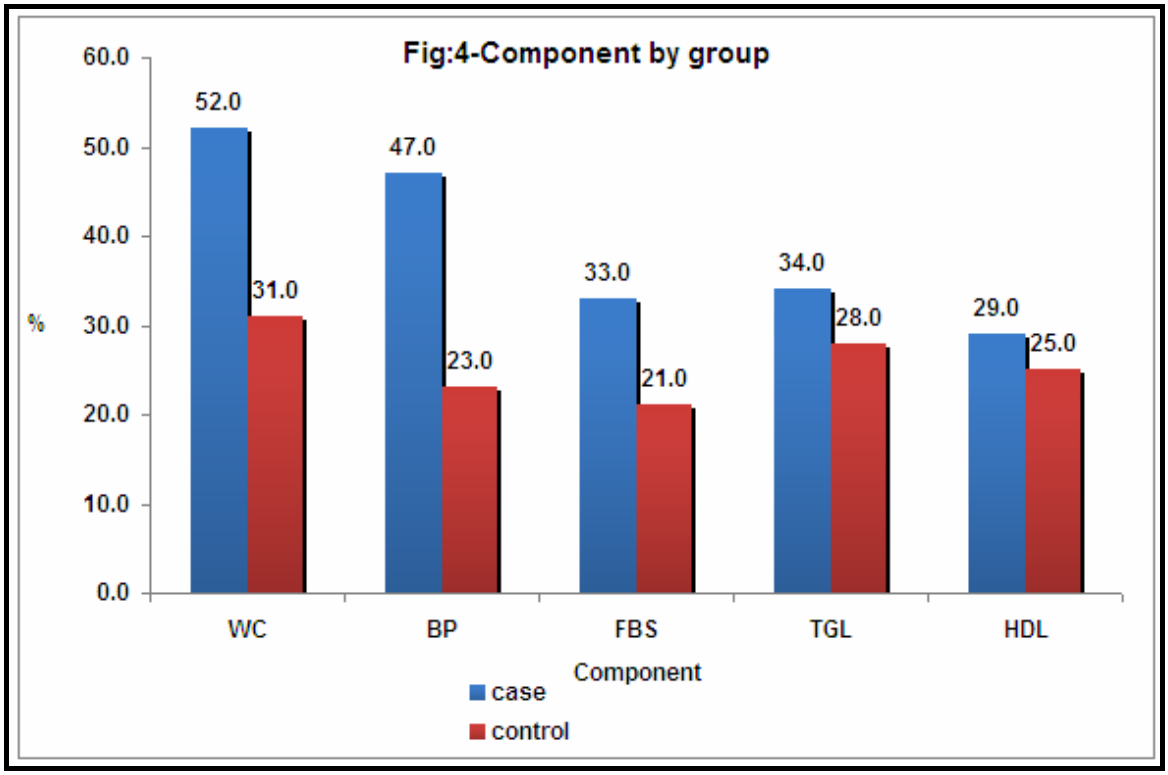
Here the proportion of metabolic syndrome was significantly (P-value <0.05) higher (46% Vs 24%) in Cases when compared to Control. So patients with metabolic syndrome has higher chances of getting nephrolithiasis

The components of metabolic syndrome were waist circumference, blood pressure, fasting blood sugar, serum triglycerides and serum high density lipoprotein. Each component of the metabolic syndrome was compared between cases (Group 1) and control (Group 2). The proportion of each component of metabolic syndrome was given in Table: 4. and in Fig: 4.

Table: 4- Distribution of basic characteristics and abnormalities of metabolic syndrome components by Case and control

Variabble	Case(N=100)	Control(N=100)	P-value
Mean Age	38.2±9.67	35.6±10.9	0.074
Mean Stone size	1.58±0.51	-	-
SEX			
Male(%)	53	52	1.000
Female(%)	47	48	
ABNORMALITIES			
WC(%)	52	31	0.004
BP(%)	47	23	0.001
FBS(%)	33	21	0.079
TGL(%)	34	28	0.445
HDL(%)	29	25	0.633
Metabolic syndrome(%)	42	26	0.025

P-value<0.05 was significant. TGL-Triglycerides, HDL- High density lipoprotein, WC-Waist Circumference, BP- Blood Pressure, FBS- Fasting Blood Sugar.



WC-waist circumference, BP-blood pressure, FBS-fasting blood sugar, TGL-triglycerides, HDL-high density lipoprotein

All components of metabolic syndrome were increased in cases when compared to control. Waist circumference component was 52% in cases and 31% in control. Blood pressure component was 47% in cases and 23% in control. Fasting blood sugar component was 33%in cases and 21% in control. Serum triglycerides were 34%in cases and 28% in control. Serum HDL was 29% in cases and 25% in control. Each component was tested separately for significance by chi square test.

WAIST CIRCUMFERENCE

The waist circumference component accounts to 52% in nephrolithiasis (cases) and 31% in control group and were tested for significance. (Table: 5)

Table: 5- Waist Circumference group

			Waist Circumference group		**Total**
			Normal (m<90cm, f<80cm)	**Abnormal (m>=90cm, f>=80cm)**	
Group	Case	Count	48	52	100
		% within Group	48.0%	52.0%	100.0%
	Control	Count	69	31	100
		% within Group	69.0%	31.0%	100.0%
Total		Count	117	83	200
		% within Group	58.5%	41.5%	100.0%

Normal - <90cm in Males, <80cm in Females.
Abnormal - ≥ 90cm in Males, ≥ 80cm in Females

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.082a	1	.003		
Continuity Correction b	8.238	1	.004		
Likelihood Ratio	9.161	1	.002		
Fisher's Exact Test				0.004	0.002
Linear-by-Linear Association	9.037	1	.003		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 41.50.

b. Computed only for a 2x2 table

The proportion of waist circumference component was significantly (P-value < 0.05) higher (52%Vs31%) in cases when compared to control.

BLOOD PRESSURE COMPONENT

The Blood pressure component accounts to 47% in nephrolithiasis (cases) and 23% in control group and were tested for significance. (Table: 6)

Table: 6 Blood Pressure component group

			Blood Pressure group		**Total**
			Normal (sbp<130|dbp <85mm/Hg)	**Abnormal (sbp>130|dbp >85mm/Hg)**	
Group	Case	Count	53	47	100
		% within Group	53.0%	47.0%	100.0%
	Control	Count	77	23	100
		% within Group	77.0%	23.0%	100.0%
Total		Count	130	70	200
		% within Group	65.0%	35.0%	100.0%

sbp-systolic blood pressure, dbp- diastolic blood pressure
Normal- Sbp <130mmHg, dbp <85mmHg
Abnormal- Sbp ≥130mmHg, dbp ≥ 85mmHg

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.659a	1	.000		
Continuity Correction b	11.626	1	.001		
Likelihood Ratio	12.854	1	.000		
Fisher's Exact Test				0.001	.000
Linear-by-Linear Association	12.596	1	.000		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 35.00.

b. Computed only for a 2x2 table, sbp-systolic blood pressure, dbp- diastolic blood pressure

The proportion of blood pressure component was significantly (P-value<0.05) higher (47%Vs23%) in nephrolithiasis (cases) group compared to control group.

FASTING BLOOD SUGAR COMPONENT

The Fasting Blood sugar component accounts to 33% in nephrolithiasis (cases) and 21% in control group and were tested for significance. (Table: 7)

Table: 7- Fasting Blood Sugar group

			Fasting Blood Sugar group		**Total**
			Normal FBS <100 mg/dl	**Abnormal FBS ≥100 mg/dl**	
Group	Case	Count	67	33	100
		% within Group	67.0%	33.0%	100.0%
	Control	Count	79	21	100
		% within Group	79.0%	21.0%	100.0%
Total		Count	146	54	200
		% within Group	73.0%	27.0%	100.0%

FBS- Fasting Blood Surgar

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.653a	1	.056		
Continuity Correction b	3.070	1	.080		
Likelihood Ratio	3.676	1	.055		
Fisher's Exact Test				0.079	0.040
Linear-by-Linear Association	3.635	1	.057		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 27.00.

b. Computed only for a 2x2 table

In fasting blood sugar component, though it was not statistically (P-value>0.05) significant, the proportion of elevated fasting blood sugar was relatively higher (33%Vs21%) in the cases.

SERUM TRIGLYCERIDES COMPONENT

The serum triglycerides' component accounts to 34% in nephrolithiasis (cases) and 28% in control group and were tested for significance. (Table: 8)

Table: Serum TGL group

			Serum TGL group		Total
			Normal <150mg/dl	**Abnormal >=150 mg/dl**	
Group	Case	Count	66	34	100
		% within Group	66.0%	34.0%	100.0%
	Control	Count	72	28	100
		% within Group	72.0%	28.0%	100.0%
Total		Count	138	62	200
		% within Group	69.0%	31.0%	100.0%

TGL- Triglycerides

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.842a	1	.359		
Continuity Correction b	.584	1	.445		
Likelihood Ratio	.843	1	.359		
Fisher's Exact Test				0.445	0.222
Linear-by-Linear Association	.837	1	.360		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 31.00.

b. Computed only for a 2x2 table

Though here in the serum triglycerides component was not statistically (P-value >0.05) significant, the proportion of elevated serum triglycerides component was relatively higher in the cases.

SERUM HDL COMPONENT

The serum HDL component accounts to 29% in nephrolithiasis (cases) and 25% in control group and were tested for significance. (Table: 9)

Table: 9 - Serum HDL group

			Serum HDL group		Total
			Normal (m<=40| f<=50mg/dl)	**Abnormal (m>40| f>50 mg/dl)**	
Group	Case	Count	71	29	100
		% within Group	71.0%	29.0%	100.0%
	Control	Count	75	25	100
		% within Group	75.0%	25.0%	100.0%
Total		Count	146	54	200
		% within Group	73.0%	27.0%	100.0%

HDL- High Density Lipoprotein
m- Male, f- Female.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.406a	1	.524		
Continuity Correction b	.228	1	.633		
Likelihood Ratio	.406	1	.524		
Fisher's Exact Test				.633	.317
Linear-by-Linear Association	.404	1	.525		
N of Valid Cases b	200				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 27.00.

b. Computed only for a 2x2 table

Though here in the serum HDL component was not statistically (P-value >0.05) significant, the proportion of serum HDL component was relatively higher in the cases.

DISTRIBUTION OF METABOLIC COMPONENTS BY GROUPS

The groups with nephrolithiasis (cases) and the controls were cross tabulated by distribution of the components of metabolic syndrome and this was tested for significance. (Table: 10)

Table:10 - Syndrome

			syndrome						Total
			0	**1**	**2**	**3**	**4**	**5**	
Group	Case	Count	30	14	14	19	19	4	100
		% within Group	30.0%	14.0%	14.0%	19.0%	19.0%	4.0%	100.0%
	Control	Count	42	21	11	19	7	0	100
		% within Group	42.0%	21.0%	11.0%	19.0%	7.0%	.0%	100.0%
Total		Count	72	35	25	38	26	4	200
		% within Group	36.0%	17.5%	12.5%	19.0%	13.0%	2.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	13.298a	5	.021
Likelihood Ratio	15.079	5	.010
Linear-by-Linear Association	9.476	1	.002
N of Valid Cases	200		

a. 2 cells (16.7%) have expected count less than 5. The minimum expected count is 2.00.

The proportion of more than three components of metabolic syndrome was significantly increased in cases group. There was a significant increasing trend was observed as the metabolic components increases in cases. This was statistically significant (P-value<0.05) by linear by linear association.

DISCUSSION

Nephrolithiasis is a common disorder affecting the urinary tract. The morbidity produced by nephrolithiasis to the patients and the huge amount spend on the diagnosis, treatment and follow up leads to search for preventive strategies of nephrolithiasis.

Due to globalization of economy and increased availability of easy life style commodities there was increased prevalence of metabolic syndrome in our community. Gupta R et al[61] on their population based study in north India showed that there is low prevalence of metabolic syndrome during adolescence age and very rapid increase in metabolic syndrome prevalence above age of 30.He called for urgent interventions to prevent epidemic of metabolic syndrome. Sedentary life habit, increased intake of animal proteins and salted food and lack of exercise leads to obesity, hypertension, type two diabetes mellitus and dylipidemia. These causes increased risk of developing cardiovascular disease and nephrolithiasis.

Sakhaee et al[42] first described the association of diabetes mellitus with uric acid calculus formation in 2002. He suggested decreased ammonia formation in the kidney due to insulin

resistance was the cause of acidic urine and uric acid calculus formation. There were many international studies describing the association of metabolic syndrome with nephrolithiasis. Till date no study was available comparing this association in our part of the country.

This study was conducted to evaluate the association of metabolic syndrome in nephrolithiasis patient population in our part of country. In this study patients with nephrolithiasis (Cases) was compared with persons without nephrolithiasis (Control) for the presence of metabolic syndrome. We also compared the association of individual component of metabolic syndrome between cases and controls.

The present study demonstrated highly significant (P-value<0.05) association of metabolic syndrome in nephrolithiasis patients when compared to control group (42% Vs 26%). Jeong IG[62] et al in their cross sectional study of 34,895 persons who underwent general health screening observed nephrolithiasis in 2.4% and metabolic syndrome in 13.7% of the screened population. He demonstrated significant association of metabolic syndrome in nephrolithiasis group with OR of 1.25. Kim YJ et al[63] demonstrated significant association of metabolic syndrome in the patients having

renal calculus (15.9% Vs 11%) when compared to individuals without renal calculus. Rendina D[64] et al in their study of data's of inpatients in southern Italy showed significant association of metabolic syndrome in renal calculus patients. He observed metabolic syndrome in 31% of the inpatient population. The present study also shows significant association in patient population.

The present study shows significant association between components of metabolic syndrome with nephrolithiasis when compared with control. The metabolic component hypertension has statistically (P-value<0.05) significant association with nephrolithiasis (47% Vs 23%) when compared with control. This association was also observed by Kim YJ[63] et al with a odd ratio of 1.08 for males and 1.24 for females. Jeong IG[62] et al observed statistic significance association between nephrolithiasis and increased waist circumference. In this study we demonstrated statistic significant (P-value<0.05) association of increased waist circumference (52% Vs 31%) between nephrolithiasis (cases) and control groups.

Though there was no statistic significant association shown for increased fasting blood sugar, increased serum triglycerides and decreased HDL between cases and control, the proportions of these

components were high in nephrolithiasis group when compared to control. Taylor EN[65] et al demonstrated increased incidence of nephrolithiasis in diabetes mellitus patients and was probably due to insulin resistance.

Kohjimoto Y[66] et al observed increased in metabolic syndrome traits with severity of renal calculus disease. We also observed increasing trends of components of metabolic syndrome in nephrolithiasis group.

The present study has significant clinical implication in public health care in the prevention of formation of nephrolithiasis. Since metabolic syndrome prevalence is increasing in our community, it is very important to formulate policies to prevent and treat this syndrome. For the treatment of metabolic syndrome there were no randomized control trials oriented guidelines available. The initial treatments of metabolic syndrome were changes in lifestyle and diet modifications. Sedentary life style habits should be discouraged even from childhood. More activities should be included in the daily schedule like regular walking, minimum of thirty minutes exercise. Diets rich in fat or animal protein or salted foods should be restricted. Diets rich in vegetables, fruits, grains, legumes and low or no fat were encouraged. Controlled weight

reduction is advised in order to prevent increased risk of developing calculus by marked weight reduction programs like bariatric surgery. Pharmacological treatment for hypertension, diabetes and dyslipidemia can be taken for control of metabolic syndrome.

The limitations of this study were stone composition in metabolic syndrome positive cases was not analysed, the change in urinary constituents in metabolic syndrome positive patients was not correlated, the duration of metabolic syndrome was not correlated with occurrence of nephrolithiasis and was not a longitudinal study, so causal relationship is not established.

CONCLUSION

The conclusions of this study are

- Metabolic syndrome is significantly associated with nephrolithiasis

- Of the components of metabolic syndrome a statistically significant association with nephrolithiasis is noted for increased waist circumference and hypertension.

- In the present study the other three components of metabolic syndrome namely diabetes mellitus, increased serum triglycerides and decreased serum HDL were found to be statistically insignificant with regard to nephrolithiasis.

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APPENDIX-1
INFORMED CONSENT FORM

Title of the study: "A study of association between metabolic syndrome and nephrolithiasis"

Name of the Participant:

Name of the Principal (Co-Investigator): Dr.N.Suresh Kumar

Name of the Institution: Rajiv Gandhi Govt General Hospital, Chennai – 3

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice; hereby give my consent to be included as a participant in" A study of association between metabolic syndrome and nephrolithiasis"

1) I have read and understood this consent form and the information provided to me.

2) I have had the consent document explained to me.

3) I have been explained about the nature of the study.

4) I have been explained about my rights and responsibilities by the investigator.

5) I have been informed the investigator of all the treatments I am taking or have taken in the past 3 months including any native (alternative) treatment.

6) I have been advised about the risks associated with my participation in this study.

7) I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8) I have not participated in any research study within the past 6 month(s)

9) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

10) I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

11) I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

12) I have understand that my identity will be kept confidential if my data are publicly presented

13) I have had my questions answered to my satisfaction.

14) I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____
Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____
Signature_____ Date_____

Address and contact number of the impartial witness:
_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____
Signature_____ Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

சிறுநீரக கல் உள்ளவருக்கும் அனுசேபபிணி உள்ளவருக்கும் (மெடபோலிக் சிண்றோம்) உள்ள பிணைப்பு பற்றிய ஆராய்ச்சி

பெயர் : தேதி :

வயது : உள்நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கம் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

சிறுநீரககல் உள்ளவருக்கும் அனுசேபபிணி உள்ளவருக்கும்(மெடபோலிக்சிண்றோம்) உள்ள பிணைப்பு பற்றிய ஆராய்ச்சிக்கு தேவையான அணைத்து விவரங்களையும் தெரியபடுத்துவதற்கு முழு சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்ரி என் சொந்த விருப்பத்தின் பேரில் தான் பங்குபெருகிறேன் மற்றும் இந்த ஆராய்ச்சியில் இருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியின் தகவல்களையும் முடிவுகளையும் அறிவியல் நோக்கத்திற்காக பயன்படுத்துவதற்கு நான் அனுமதிக்கிறேன். நான் இந்த ஆராய்ச்சியில் பங்கு பெற சம்மதிக்கிறேன்.

பங்கேற்பவர் பெயர் : பங்கேற்பவர் கையொப்பம்

(அ) இடது கட்டைவிரல் ரேகை

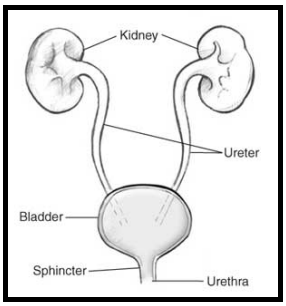
ஆய்வாளர் பெயர் : ஆய்வாளர் கையொப்பம்

APPENDIX-2
PROFORMA

Name: Age/Sex:

IP /OP number: Occupation:

Presence of nephrolithiasis:



Waist circumference:

Blood pressure:

Blood fasting sugar:

Serum triglycerides:

Serum HDL:

Inference:

A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of the degree of

M.Ch (UROLOGY) – BRANCH – IV

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY CHENNAI

AUGUST 2013

DECLARATION

I solemnly declare that this dissertation titled **"A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS"** was prepared by me in the Department of Urology, Madras Medical College and Rajiv Gandhi Government General Hospital, Park town, Chennai - 3 under the able guidance and supervision of **Prof.R.Jeyaraman, M.S., M.Ch (Uro).,** Professor & Head of the Department, Department of Urology, Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch. Urology.

Dr.SURESH KUMAR.N

Place: Chennai
Date:

CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS"** submitted by **Dr.Suresh Kumar.N** appearing for **M.Ch. (Urology)** degree examination in August 2013, is a bonafide record of work done by him under my guidance and supervision in fulfillment of requirement of The Tamil Nadu Dr.M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

Prof.R.Jeyaraman, M.S. M.Ch,
Professor & Head of the Department,
Department of Urology,
Rajiv Gandhi Government General Hospital,
Madras Medical College,
Chennai -600003.

The Dean
Madras Medical College,
Chennai -600003

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Last, but not least, I thank my fellow past and present postgraduates who helped me in carrying out my work and preparing this manual.

INDEX

APPENDIX-3

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. N. Suresh Kumar
PG in MCh Urology
Madras Medical College, Chennai -3

Dear Dr. N. Suresh Kumar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study of association between metabolic syndrome and nephrolithiasis " No.25032012.

The following members of Ethics Committee were present in the meeting held on 22.03.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer
6.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

APPENDIX-5
ABBREVIATION

CT	:	Computed Tomography
USG	:	Ultrasonogram
WC	:	Waist Circumference
FBS	:	Fasting Blood Sugar
SBP	:	Systolic Blood Pressure
DBP	:	Diastolic Blood Pressure
TGL	:	Triglycerides
HDL	:	High Density Lipoprotein
MSC	:	Metabolic Syndrome Components

CONTROLS WITHOUT NEPHROLITHIASIS

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
1	2	Arumugam	36	1	-	-	106	1	120	84	0	88	0	168	1	36	1	3	3
2	2	Sakthivel	25	1	-	-	83	0	110	70	0	82	0	120	0	46	0	0	0
3	2	Manoharan	49	1	-	-	88	0	150	90	1	96	0	142	0	48	0	1	1
4	2	Kamala Kannan	33	1	-	-	108	1	120	80	0	87	0	134	0	42	0	1	1
5	2	Selvi	40	2	-	-	110	1	140	100	1	160	1	142	0	56	0	3	3
6	2	Gajendran	32	1	-	-	82	0	120	80	0	90	0	130	0	48	0	0	0
7	2	Jeya kumar	42	1	-	-	88	0	120	80	0	96	0	146	0	38	1	1	1
8	2	Rekha	26	2	-	-	76	0	110	70	0	78	0	130	0	56	0	0	0
9	2	Laxmi	32	2	-	-	96	1	120	80	0	89	0	138	0	54	0	1	1
10	2	Amudha	36	2	-	-	102	1	140	92	1	156	1	140	0	60	0	3	3
11	2	Ramu	25	1	-	-	86	0	120	70	0	92	0	132	0	48	0	0	0
12	2	Ragammal	65	2	-	-	77	0	120	80	0	90	0	143	0	54	0	0	0
13	2	Saraswathi	40	2	-	-	76	0	120	80	0	146	1	144	0	58	0	1	1
14	2	Kamala	32	2	-	-	76	0	120	80	0	82	0	132	0	62	0	0	0
15	2	Gopi	28	1	-	-	99	1	120	86	0	88	0	212	1	46	0	2	2
16	2	Prabhu	25	1	-	-	80	0	110	70	0	86	0	136	0	42	0	0	0
17	2	Roopavathy	48	2	-	-	74	0	120	80	0	94	0	130	0	56	0	0	0
18	2	Pandian	47	1	-	-	88	0	160	96	1	88	0	158	1	52	0	2	2
19	2	Shanthalaxmi	30	2	-	-	78	0	120	80	0	82	0	122	0	52	0	0	0
20	2	Rajendran	44	1	-	-	102	1	150	100	1	96	0	178	1	38	1	4	4
21	2	Mariammal	32	2	-	-	78	0	120	80	0	108	1	132	0	56	0	1	1
22	2	Ramu	30	1	-	-	86	0	120	80	0	146	1	144	0	58	0	1	1
23	2	Murugan	46	1	-	-	88	0	120	80	0	86	0	132	0	48	0	0	0
24	2	Nagaraj	25	1	-	-	84	0	120	80	0	89	0	122	0	52	0	0	0
25	2	Shanthi	36	2	-	-	104	1	110	70	0	98	0	134	0	58	0	1	1
26	2	Govindasamy	46	1	-	-	96	1	140	98	1	96	0	146	0	42	0	2	2
27	2	Rajesh	22	1	-	-	78	0	120	80	0	92	0	148	0	48	0	0	0
28	2	Rajamani	47	2	-	-	101	1	150	90	1	78	0	156	1	52	0	3	3
29	2	Nagammal	26	2	-	-	78	0	110	80	0	78	0	128	0	62	0	0	0
30	2	Ravi	52	1	-	-	102	1	150	100	1	148	1	146	0	38	1	4	4
31	2	Vasanthakumari	36	2	-	-	104	1	120	80	0	132	1	156	1	48	1	4	4
32	2	Varadaraj	24	1	-	-	82	0	120	80	0	78	0	134	0	46	0	0	0
33	2	Arul	40	1	-	-	101	1	150	90	1	134	1	146	0	48	0	3	3
34	2	Nandakumar	30	1	-	-	88	0	120	80	0	88	0	133	0	44	0	0	0
35	2	Indradevi	30	2	-	-	78	0	140	90	1	92	0	134	0	58	0	1	1
36	2	Chinna thai	60	2	-	-	76	0	160	100	1	134	1	140	0	52	0	2	2
37	2	Poomadhu	48	2	-	-	103	1	120	80	0	89	0	192	1	44	1	3	3
38	2	Murugesan	58	1	-	-	88	0	120	80	0	88	0	132	0	43	0	0	0

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
39	2	Rajesh	32	1	-	-	97	1	120	80	0	92	0	154	1	48	0	2	2
40	2	Jeyanthi	37	2	-	-	94	1	120	80	0	122	1	154	1	54	0	3	3
41	2	Sheela	37	2	-	-	79	0	120	80	0	98	0	146	0	52	0	0	0
42	2	Ekambaram	43	1	-	-	88	0	160	90	1	202	1	146	0	46	0	2	2
43	2	Lilly	33	2	-	-	77	0	120	80	0	86	0	138	0	38	0	0	0
44	2	Velmurugan	38	1	-	-	87	0	120	80	0	90	0	140	0	46	0	0	0
45	2	Ponni	37	2	-	-	76	0	120	80	0	88	0	130	0	56	0	0	0
46	2	Madhan	22	1	-	-	88	0	110	80	0	78	0	128	0	52	0	0	0
47	2	Kanagaraj	55	1	-	-	82	0	150	90	1	172	1	180	1	38	1	4	4
48	2	Rani	50	2	-	-	78	0	140	90	1	92	0	168	1	54	0	2	2
49	2	Raji	27	1	-	-	86	0	120	80	0	88	0	134	0	48	0	0	0
50	2	Puspha	22	2	-	-	78	0	110	70	0	76	0	122	0	60	0	0	0
51	2	Laxmi	33	2	-	-	78	0	120	80	0	89	0	128	0	54	0	0	0
52	2	Fernandes	26	1	-	-	103	1	120	80	0	90	0	172	1	34	1	3	3
53	2	Faritha	25	2	-	-	76	0	120	80	0	84	0	130	0	62	0	0	0
54	2	Yuvaraj	20	1	-	-	82	0	110	70	0	80	0	128	0	56	0	0	0
55	2	Babu	53	1	-	-	104	1	160	90	1	126	1	146	0	32	1	4	4
56	2	Latha	21	2	-	-	72	0	110	80	0	86	0	126	0	58	0	0	0
57	2	Arul kumar	23	1	-	-	85	0	120	70	0	90	0	162	1	38	1	2	2
58	2	Shabena	28	2	-	-	109	1	150	90	1	142	1	146	0	54	0	3	3
59	2	Sumithra	21	2	-	-	72	0	120	80	0	82	0	134	0	58	0	0	0
60	2	Senthil kumar	26	1	-	-	86	0	120	80	0	94	0	168	1	39	1	2	2
61	2	Mohammed Azar	24	1	-	-	80	0	120	80	0	80	0	134	0	44	0	0	0
62	2	Kala	30	2	-	-	77	0	120	80	0	86	0	136	0	58	0	0	0
63	2	Marimuthu	34	1	-	-	84	0	120	80	0	97	0	158	1	46	0	1	1
64	2	Menaga	24	2	-	-	74	0	120	80	0	94	0	156	1	52	0	1	1
65	2	Anandan	37	1	-	-	87	0	120	80	0	89	0	146	0	46	0	0	0
66	2	Laxmi	55	2	-	-	74	0	120	90	0	204	1	192	1	38	1	3	3
67	2	Mani	38	1	-	-	85	0	120	80	0	92	0	202	1	36	1	2	2
68	2	Vijaya rangan	39	1	-	-	82	0	120	84	0	98	0	198	1	32	1	2	2
69	2	chandrika	35	2	-	-	74	0	120	80	0	80	0	134	0	56	0	0	0
70	2	Ramu	51	1	-	-	80	0	150	90	1	122	1	182	1	32	1	4	4
71	2	Malarkodi	27	2	-	-	73	0	120	80	0	84	0	140	0	54	0	0	0
72	2	Vasantha	55	2	-	-	71	0	120	80	0	132	1	167	1	46	1	3	3
73	2	Sabeer	23	1	-	-	88	0	120	80	0	88	0	146	0	46	0	0	0
74	2	Ikram Hussain	27	1	-	-	87	0	120	80	0	128	1	180	1	38	1	3	3
75	2	Selvi	35	2	-	-	98	1	140	90	1	80	0	158	1	54	0	3	3
76	2	Balaji	31	1	-	-	82	0	120	80	0	92	0	140	0	48	0	0	0
77	2	Sarasa	55	2	-	-	74	0	120	80	0	86	0	143	0	44	1	1	1
78	2	Janaki	48	2	-	-	102	1	150	90	1	190	1	142	0	54	0	3	3

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
79	2	Natarajan	30	1	-	-	86	0	120	80	0	78	0	140	0	52	0	0	0
80	2	Perumal	60	1	-	-	83	0	120	80	0	94	0	138	0	48	0	0	0
81	2	Rani	51	2	-	-	75	0	120	80	0	131	1	134	0	56	0	1	1
82	2	Dharmaraj	28	1	-	-	105	1	120	80	0	92	0	184	1	36	1	3	3
83	2	Sharmila	53	2	-	-	74	0	124	80	0	80	0	138	0	62	0	0	0
84	2	Vetri	21	1	-	-	78	0	120	80	0	90	0	142	0	60	0	0	0
85	2	Raman	36	1	-	-	88	0	140	90	1	86	0	186	1	32	1	3	3
86	2	Anjalai	26	2	-	-	96	1	120	80	0	87	0	140	0	56	0	1	1
87	2	Arjunan	28	1	-	-	86	0	124	80	0	90	0	130	0	46	0	0	0
88	2	Gowri	33	2	-	-	75	0	120	80	0	86	0	128	0	58	0	0	0
89	2	Suresh	23	1	-	-	87	0	124	80	0	88	0	158	1	46	0	1	1
90	2	Paranthaman	40	1	-	-	106	1	140	90	1	89	0	139	0	36	1	3	3
91	2	Devika	45	2	-	-	101	1	122	80	0	86	0	156	1	46	1	3	3
92	2	Nandini	21	2	-	-	78	0	110	80	0	84	0	126	0	62	0	0	0
93	2	Prabakaran	22	1	-	-	100	1	140	100	1	96	0	190	1	36	1	4	4
94	2	Minalla	40	2	-	-	95	1	140	96	1	112	1	142	0	54	0	3	3
95	2	Devi	36	2	-	-	98	1	120	80	0	82	0	134	0	64	0	1	1
96	2	Venkatesh	26	1	-	-	84	0	120	80	0	84	0	138	0	34	1	1	1
97	2	Bhuvaneswari	48	2	-	-	96	1	120	80	0	92	0	140	0	56	0	1	1
98	2	Jayachithra	31	2	-	-	90	1	110	70	0	84	0	130	0	62	0	1	1
99	2	Prabhu	27	1	-	-	86	0	120	80	0	78	0	142	0	38	1	1	1
100	2	Akilandeswari	37	2	-	-	96	1	120	80	0	92	0	138	0	58	0	1	1

Group-1: Individuals with Nephrolithiasis, Group-2: Individuals without Nephrolithiasis, WC- Waist Circumference, SBP- Systolic Blood Pressure DPB- Diastolic Blood Pressure, FBS- Fasting Blood Sugar, TGL- Triglycerides, HDL- High Density Lipoprotein, MSC- Metabolic Syndrome Components

APPENDIX-IV
MASTER CHART
CASES GROUP WITH NEPHROLITHIASIS

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
1	1	Vanitha	25	2	LEFT	1.8	76	0	120	80	0	86	0	138	0	58	0	0	0
2	1	Arjunan	31	1	RIGHT	2.2	102	1	150	90	1	89	0	168	1	36	1	4	4
3	1	Kishore kumar	22	1	LEFT	1.6	88	0	120	80	0	80	0	142	0	42	0	0	0
4	1	Ramu	35	1	RIGHT	2	86	0	150	100	1	84	0	146	0	36	1	2	2
5	1	Manikandan	25	1	LEFT	1.5	105	1	120	80	0	90	0	132	0	42	0	1	1
6	1	Sussela	45	2	RIGHT	1.8	102	1	160	100	1	124	1	156	1	48	1	5	5
7	1	Srinivasan	35	1	RIGHT	2	87	0	120	80	0	230	1	142	0	56	0	1	1
8	1	Siddique	38	1	RIGHT	1.5	102	1	150	100	1	132	1	156	1	48	0	4	4
9	1	Basheer	45	1	RIGHT	2	82	0	124	80	0	86	0	134	0	48	0	0	0
10	1	Nithiyanantham	46	1	LEFT	1.8	106	1	140	90	1	82	0	134	0	46	0	2	2
11	1	Laxmi	30	2	LEFT	1.5	74	0	120	80	0	92	0	130	0	58	0	0	0
12	1	Pitchai	40	1	LEFT	1.7	98	1	140	90	1	138	1	137	0	38	1	4	4
13	1	Devaki	32	2	RIGHT	2.1	94	1	140	90	1	94	0	142	0	44	1	3	3
14	1	Banumathi	35	2	RIGHT	2.8	78	0	120	80	0	89	0	132	0	56	0	0	0
15	1	Subramani	42	1	RIGHT	1.9	85	0	140	100	1	204	1	168	1	32	1	4	4
16	1	Sathya	26	2	RIGHT	1.1	72	0	120	80	0	86	0	128	0	54	0	0	0
17	1	Maniyan	39	1	RIGHT	1.2	89	0	120	80	0	89	0	142	0	48	0	0	0
18	1	Dakchinamoorthy	53	1	LEFT	2.5	88	0	140	90	1	108	1	172	1	36	1	4	4
19	1	Jeganathan	31	1	LEFT	1.8	97	1	120	80	0	86	0	142	0	34	1	2	2
20	1	Rajalaxmi	35	2	LEFT	1	96	1	140	90	1	110	1	142	0	52	0	3	3
21	1	Lakshmi	47	2	RIGHT	1.9	90	1	150	100	1	126	1	162	1	43	1	5	5
22	1	Manoj	30	1	RIGHT	1	86	0	124	80	0	86	0	156	1	38	1	2	2
23	1	Subramani	42	1	RIGHT	1.5	85	0	120	80	0	78	0	142	0	54	0	0	0
24	1	Sasikala	24	2	LEFT	1.9	78	0	140	100	1	86	0	154	1	46	1	3	3
25	1	Laxmanan	32	1	LEFT	1.4	86	0	120	80	0	92	0	130	0	48	0	0	0
26	1	Vijaya	43	2	LEFT	1.1	106	1	160	100	1	129	1	180	1	52	0	4	4
27	1	Jayachandran	25	1	LEFT	1	88	0	120	80	0	80	0	140	0	50	0	0	0
28	1	Banu	43	2	RIGHT	1.1	92	1	140	90	1	98	0	172	1	46	1	4	4
29	1	Dakchinamoorthy	55	1	LEFT	1.3	86	0	160	100	1	86	0	142	0	48	0	1	1
30	1	Senthil nathan	45	1	RIGHT	0.8	99	1	120	80	0	142	1	174	1	42	0	3	3
31	1	Venkata Ramani	27	2	RIGHT	1.4	96	1	120	80	0	90	0	132	0	62	0	1	1
32	1	Bhavani	45	2	LEFT	1.8	92	1	150	100	1	122	1	157	1	52	0	4	4
33	1	Muthu	36	1	RIGHT	3	94	1	140	90	1	80	0	172	1	38	1	4	4
34	1	Chithra	33	2	LEFT	1.3	97	1	120	80	0	96	0	142	0	56	0	1	1
35	1	Inbasakaran	20	1	RIGHT	1.3	86	0	120	80	0	78	0	132	0	46	0	0	0
36	1	Kumar	35	1	RIGHT	1.6	103	1	150	100	1	114	1	164	1	44	0	4	4
37	1	Balasundari	28	2	RIGHT	1.3	102	1	140	90	1	120	1	132	0	52	0	3	3
38	1	Venkatesan	23	1	LEFT	1.4	78	0	120	80	0	88	0	164	1	38	1	2	2

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
39	1	Balasubramaniyam	29	1	LEFT	1.2	104	1	140	90	1	128	1	168	1	48	0	4	4
40	1	Gnanasekari	25	2	RIGHT	1.3	76	0	120	80	0	90	0	130	0	56	0	0	0
41	1	Gandhimathi	46	2	RIGHT	1.5	98	1	160	100	1	134	1	159	1	54	0	4	4
42	1	Ramlingam	24	1	RIGHT	1.2	82	0	120	80	0	80	0	141	0	46	0	0	0
43	1	Baskar	38	1	RIGHT	1.6	107	1	140	90	1	94	0	162	1	39	1	4	4
44	1	Jessy Jane	38	2	LEFT	1.1	88	1	140	90	1	129	1	138	0	56	0	3	3
45	1	Arumugam	48	1	RIGHT	1.7	97	1	140	100	1	132	1	192	1	30	1	5	5
46	1	Kannagi	40	2	LEFT	0.8	98	1	140	100	1	128	1	146	0	51	0	3	3
47	1	Munusamy	24	1	LEFT	1	86	0	140	90	1	86	0	188	1	42	0	2	2
48	1	Cornalius	30	1	LEFT	1.9	106	1	150	90	1	86	0	142	0	42	0	2	2
49	1	Raju	38	1	RIGHT	2.6	96	1	140	90	1	94	0	169	1	49	0	3	3
50	1	Saraswathy	55	2	RIGHT	1.1	96	1	120	80	0	78	0	132	0	60	0	1	1
51	1	Krishnamoorthy	32	1	RIGHT	2	88	0	140	90	1	80	0	162	1	46	0	2	2
52	1	Krishnamoorthi	49	1	LEFT	1.3	108	1	148	100	1	126	1	198	1	38	1	5	5
53	1	Somasundaram	34	1	RIGHT	1.8	88	0	120	80	0	86	0	128	0	54	0	0	0
54	1	Nagasundari	30	2	RIGHT	1	96	1	120	80	0	90	0	140	0	56	0	1	1
55	1	Ponni	35	2	RIGHT	3.2	78	0	110	70	0	78	0	120	0	58	0	0	0
56	1	Chinnammal	50	2	RIGHT	2	96	1	120	80	1	88	0	168	1	44	1	4	4
57	1	Rajendran	44	1	RIGHT	1.1	106	1	140	90	1	89	0	169	1	37	1	4	4
58	1	Sukumari	29	2	LEFT	2	79	0	110	80	0	74	0	122	0	60	0	0	0
59	1	Swaminathan	39	1	LEFT	1.4	86	0	140	100	1	80	0	128	0	52	0	1	1
60	1	Malar	52	2	RIGHT	3	97	1	150	100	1	142	1	142	0	56	0	3	3
61	1	Suresh	43	1	LEFT	1.4	86	0	120	80	0	80	0	131	0	48	0	0	0
62	1	Amira	45	2	RIGHT	2	102	1	120	80	0	164	1	169	1	52	0	3	3
63	1	Raja Mohammed	30	1	RIGHT	2.3	82	0	120	80	0	90	0	140	0	48	0	0	0
64	1	Asohan	60	1	LEFT	2.2	86	0	120	80	0	88	0	148	0	38	1	1	1
65	1	Maroof	30	1	RIGHT	2	88	0	120	80	0	86	0	138	0	46	0	0	0
66	1	Senthil kumar	30	1	LEFT	2.3	86	0	150	90	1	122	1	130	0	52	0	2	2
67	1	Kamatchi	45	2	LEFT	2.6	104	1	120	80	0	132	1	186	1	51	0	3	3
68	1	Kumari	32	2	LEFT	1.5	76	0	120	80	0	84	0	128	0	60	0	0	0
69	1	Raja Sulochana	40	2	RIGHT	1.3	88	1	150	100	1	89	0	168	1	56	0	3	3
70	1	Rajeswari	41	2	RIGHT	1.4	96	1	120	80	0	166	1	172	1	42	1	4	4
71	1	Sethu	43	1	RIGHT	1.3	82	0	150	100	1	128	1	146	0	49	0	2	2
72	1	Karthiga	26	2	RIGHT	1.3	78	0	110	70	0	84	0	138	0	58	0	0	0
73	1	Velu	29	1	LEFT	1.2	104	1	150	100	1	88	0	157	1	34	1	4	4
74	1	Raghavi	54	2	RIGHT	1.5	87	1	120	80	0	139	1	184	1	56	0	3	3
75	1	Loganathan	33	1	RIGHT	2.6	105	1	160	100	1	79	0	170	1	36	1	4	4
76	1	Pughalendhi	34	1	RIGHT	1.5	86	0	120	80	0	92	0	138	0	44	0	0	0
77	1	Vijayalakshmi	45	2	LEFT	1.6	93	1	150	96	1	162	1	136	0	56	0	3	3
78	1	Jeyamani	40	2	RIGHT	0.8	76	0	120	80	0	90	0	129	0	54	0	0	0
79	1	Mahendran	45	1	LEFT	1.8	84	0	140	90	1	136	1	132	0	48	0	2	2
80	1	Periyasamy	49	1	RIGHT	1.4	99	1	150	90	1	142	1	143	0	38	0	3	3

S.No	Group	NAME	AGEc	SEX	STONE SIDE	STONE SIZE	WAIST	WC_gp	SBP	DBP	BP_gp	FBS	FBS_gp	TGL	TGL_gp	HDL	HDL_gp	TOTAL	MSC
81	1	Veerammal	60	2	LEFT	2.2	78	0	120	80	0	120	1	136	0	46	1	2	2
82	1	Karunanithi	56	1	LEFT	1.1	83	0	120	80	0	92	0	132	0	42	0	0	0
83	1	Srinivasa Rao	34	1	RIGHT	1.4	107	1	124	80	0	84	0	138	0	49	0	1	1
84	1	Kumari	48	2	RIGHT	1.4	97	1	120	80	0	152	1	142	0	46	1	3	3
85	1	Kumara Selvi	30	2	LEFT	1.6	76	0	120	80	0	84	0	128	0	62	0	0	0
86	1	Arul	33	1	LEFT	1.6	109	1	150	100	1	97	0	134	0	46	0	2	2
87	1	Maniammal	43	2	LEFT	1.1	74	0	120	80	0	84	0	132	0	42	1	1	1
88	1	Harivel	41	1	RIGHT	1.3	80	0	122	80	0	96	0	138	0	50	0	0	0
89	1	Shanmuga Sundari	57	2	LEFT	1.4	92	1	160	100	1	90	0	142	0	42	1	3	3
90	1	Sanju	25	2	LEFT	1.7	74	0	110	70	0	86	0	128	0	62	0	0	0
91	1	Krishnaveni	47	2	RIGHT	0.8	96	1	120	80	0	82	0	124	0	62	0	1	1
92	1	Subramani	51	1	RIGHT	1.5	107	1	150	90	1	98	0	169	1	36	1	4	4
93	1	Latha	40	2	LEFT	1.5	76	0	120	80	0	86	0	140	0	54	0	0	0
94	1	Shantha	42	2	RIGHT	1.3	74	0	120	80	0	154	1	132	0	56	0	1	1
95	1	Geetha	43	2	LEFT	1.3	78	0	120	80	0	94	0	138	0	54	0	0	0
96	1	Ravi	35	1	LEFT	1.2	103	1	120	80	0	86	0	158	1	38	1	3	3
97	1	Rajammal	58	2	LEFT	1.3	78	0	120	80	0	90	0	126	0	62	0	0	0
98	1	Malathi	52	2	LEFT	1	99	1	150	100	1	186	1	132	0	59	0	3	3
99	1	Sri Kandhan	27	1	RIGHT	1.2	97	1	140	100	1	88	0	134	0	46	0	2	2
100	1	Abirami	37	2	LEFT	0.8	96	1	120	80	0	86	0	128	0	52	0	1	1